

Presentation 13 – John Grabenstein

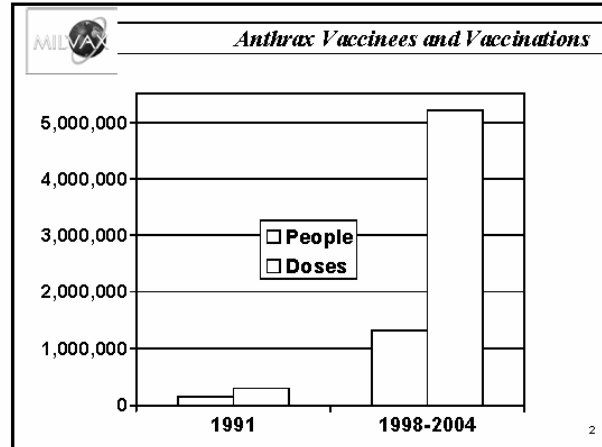
MILVAX

20 Studies to Evaluate Adverse Events After Anthrax Immunization

7 Apr 05
 COL John D. Grabenstein, RPh, PhD, U.S. Army

**Department of Veterans Affairs
 Research Advisory Committee
 on Gulf War Veterans' Illnesses**

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MILVAX *World War II Shot Records*

IMMUNIZATION REGISTER AND OTHER MEDICAL DATA
(SEE 45.6-7)

NAME (Last, First, Middle Initial) SSN
Grabenstein, Herman J Jr 0863988

DATE OF BIRTH: 22Apr21 RACE: W BLOOD GROUP: O MED. OFF.: WJH

DATE	SMALLPOX VACCINE	TYPE OF REACTION	MED. OFF.
19Nov43	1	Immune	N/A
19Oct44	1	Immune	N/A

DATE	TRIPLE TYPHOID VACCINE	TYPE OF REACTION	MED. OFF.
Comp	1		N/A
Nov42	1		N/A
19Nov43	1		N/A
19Oct44	1		N/A
88Sep45	1		N/A

IMMUNIZATION REGISTER

LAST NAME: Sandquist, Eric ARMY SERIAL NO.: 31257823

GRADE: REGT. OR STAFF CORP. AGE: RACE: W

DATE	SMALLPOX VACCINE	TYPE OF REACTION	MED. OFFICER
3 Jan 43	Vaccinoid		N/A
12 Mar 43	Vaccinoid		N/A

DATE	TRIPLE TYPHOID VACCINE	TYPE OF REACTION	MED. OFFICER
1st dose	14Jan43		N/A
2d dose	17Feb43		N/A
3d dose	10Mar43		N/A

MILVAX *Science*

Anthrax: Evidence for vaccine effectiveness

- Brachman study, 1,249 people, *Am J Public Health* 1962
- Rhesus monkeys: 62 of 65 survive inhalation challenge
- Rabbits: 114 of 117 survive inhalation challenge
- FDA decisions: 1970, 1985, 2004 Jan + Dec
- National Academy of Sciences: 2002

Anthrax: Evidence for vaccine safety

- 20 human safety studies, 34 peer-reviewed publications
- FDA decisions: 1970, 1985, 2004 Jan + Dec
- National Academy of Sciences: 2002
- ACIP-2001, CDC-2005

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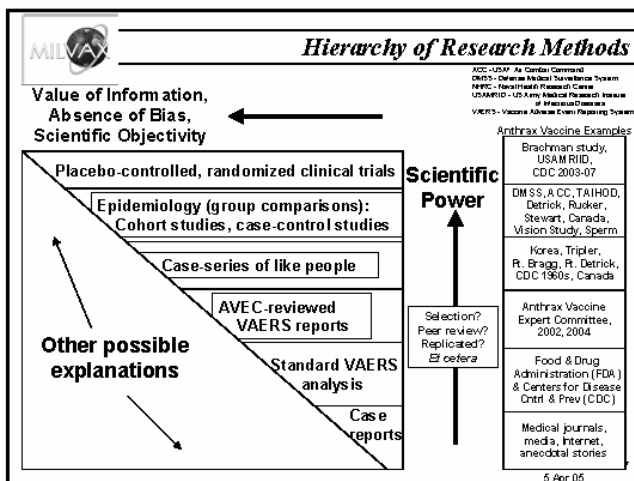
MILVAX *IOM Report, 2002, Tables 4-1, 6-1, 6-2*

	Fever	Systemic, Any	Erythema or Swelling	Pain, Any
Acellular pertussis	0 - 7%	17 - 29%	12 - 15%	51 - 77%
Hepatitis A	0 - 3%	4 - 22%	4 - 40%	40 - 52%
Hepatitis B	0 - 4%	10%	1 - 99%	11 - 43%
Influenza	1 - 13%	11 - 34%	11 - 21%	24 - 86%
Rabies	2 - 18%	3%	1 - 18%	4 - 52%
Tetanus - diphtheria (Td)	1 - 9%	17 - 26%	22 - 35%	43 - 85%
Anthrax	1 - 8%	1 - 36%	3 - 42%	Sore: 67 - 83%

www.nap.edu/catalog/10310.html 5

MILVAX *Anthrax Vaccine Safety Litany*

	Vaccinees
Brachman Study, <i>Am J Public Health</i> 1962	379
CDC Observational Study, <i>Fed Reg</i> 1985	6,986
Ft Detrick Multi-Vaccine Studies, <i>BJH# 58, Ann Intern Med</i> 1965, 1974	99
Ft Detrick Long-Term Health Study, <i>Vaccine</i> 2004	142
Fort Bragg Booster Study (after Persian Gulf War), <i>Vaccine</i> 2002	495
USAMRIID Reduced-Dose / Route-Change Study, <i>Vaccine</i> 2002	173
Fort Detrick Special Immunization Program, <i>Vaccine</i> 2001	1,583
Canadian Forces Safety Evaluation, <i>Military Medicine</i> 2004	403
TAMC-601 Survey, <i>MMMR</i> 2000; 49:341-5, <i>J Occup Environ Med</i> 2003	601
US Forces Korea Records, <i>MMMR</i> 2000; 49:341-5, <i>Vaccine</i> 2003	2,824
VAERS review by AVE C, <i>Pharmacoepidemiol & Drug Safety</i> 2002, 2004	1,623
ROTC Cadets, Ft Lewis, <i>Med Surveil Mon Rep</i> 2001	73
USAF Air Combat Command Study, <i>Military Medicine</i> 2002	4,045
Fort Stewart Pregnancy Study, <i>JAMA</i> 2002	4,092
Army Disability Discharge Claims Database, <i>J Occup Environ Med</i> 2004	154,456
USAF Visual Acuity Study	958
Aviator Flight Physical Examinations	3,356
DMSS Hospitalization Cohort Study, <i>Vaccine</i> 2002	757,540 py
NHRC Hospitalization Cohort Study, <i>Vaccine</i> 2002	120,870 py
Male Fertility Study (sperm parameters), <i>Fertility & Sterility</i> 2005	254
<i>Mycoplasma</i> Study, <i>Emerging Infectious Diseases</i> 2002	(laboratory) ⁶



MILVAX *Anthrax Vaccine Safety Surveillance*

- Mar 98 to Oct 04, > 5.2 million doses of anthrax vaccine to > 1.3 million people.
- Soreness, redness, itching, swelling at injection site:
 - Less than 2.5 cm: 30% of men, 60% of women.
 - More than 12 cm: 1% to 2%, both genders
 - Inject over deltoid (not triceps)
- Lump at injection site common, lasts a few weeks, goes away.
- Systemic symptoms—muscle or joint aches, headaches, rashes, chills, low-grade fever, nausea.
 - 5% to 35%, like other vaccines

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**Rate Ratios for Hospitalization & Anthrax Vaccination
(Hospitalization Rate Among Anthrax Vaccine Recipients
Divided by Rate Among Nonrecipients, for Active-Duty Personnel)**

Recipients = 350,296 person-years of experience
Nonrecipients = 2,368 million person-years of experience

Category	Rate per 100,000 per Year		Rate Ratios		95% Confidence Interval (Adj.)	Significant Elevation?
	Vaccinated	Unvaccinated	Unadj.	Adjusted		
Mental Health	383.1	728.7	0.52	0.58	0.54 — 0.63	no
Endocrine / Immunol.	29.1	50.7	0.57	0.69	0.58 — 0.82	no
Blood / Blood Formtn.	12.8	21.8	0.59	0.73	0.55 — 0.96	no
Musculoskeletal	432.4	708.7	0.61	0.74	0.70 — 0.79	no
/ Connective Tissue						
Ill-Defined Conditions	177.3	249.7	0.71	0.81	0.73 — 0.89	no
Respiratory	156.7	238.9	0.66	0.81	0.73 — 0.90	no
Genitourinary—Male	74.8	96.8	0.77	0.82	0.72 — 0.95	no
Neoplasms	83.4	123.1	0.65	0.85	0.71 — 1.02	no
Nervous System	61.7	91.5	0.67	0.86	0.74 — 0.99	no
Circulatory	110.2	152.9	0.72	0.88	0.79 — 0.99	no
Injury or Poisoning	555.2	580.6	0.96	0.89	0.84 — 0.94	no
Digestive	405.0	478.2	0.85	0.92	0.87 — 0.98	no
Skin	82.2	100.0	0.82	0.94	0.84 — 1.04	no
Infectious	84.5	102.7	0.82	1.01	0.90 — 1.13	no
Genitourinary-Female	895.2	822.9	1.09	1.13	0.97 — 1.32	no
Complications of Pregnancy	372.7	848.0	0.44			no

Key Finding: No category of hospitalization is elevated among anthrax vaccine recipients at a statistically significant level.


Rate ratios adjusted by standard manner (regression) to control independent effects of age, gender, rank, deployment, service, ethnicity, previous hospitalization, year, and occupation. If confidence interval includes 1.00, then difference between vaccinated and unvaccinated group is not statistically significant.

Source: *Defense Medical Surveillance System*, 10 May 2003. Data for Jan 1985 to Dec 1999.

Lange JL, et al. *Vaccine* 2003; 21 (Apr 2): 1620-28.

Institute of Medicine (IOM) Report April 2002
National Academy of Sciences, www.nap.edu/catalog/10310.html

- **EFFECTIVE:** "The committee finds that the available evidence from studies with humans and animals, coupled with reasonable assumptions of analogy, show that AVA as licensed is an effective vaccine for the protection of humans against anthrax, including inhalational anthrax, caused by all known or plausible engineered strains of *B. anthracis*."
- **SAFE:** "The committee found no evidence that people face an increased risk of experiencing life-threatening or permanently disabling adverse events immediately after receiving AVA, when compared with the general population. Nor did it find any convincing evidence that people face elevated risk of developing adverse health effects over the longer term, although data are limited in this regard (as they are for all vaccines)."
- **SAFE:** Side effects "comparable to those observed with other vaccines regularly administered to adults."



The Everyday Environment

- At a summer picnic:
 - Bacteria in unrefrigerated food
 - Abrasions sliding into 2nd base
 - High-fives after game
 - Sneezes from summer "colds"
 - Water swallowed while swimming
 - Didn't wash hands after bathroom
 - Bee sting
 - Ragweed pollen in the air
 - Poison ivy in the outfield
 - Unprotected intercourse
- At a training camp or barracks:
 - Bacteria in unrefrigerated food
 - Abrasions on obstacle course
 - High-fives after team success
 - Sneezes from summer "colds"
 - Water shared from buddy's canteen
 - Didn't wash hands after latrine
 - Bee sting
 - Ragweed pollen in the air
 - Poison ivy at the range
 - Unprotected intercourse (?)

• The human body is built to function normally amid an environment filled with multiple antigens.

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Simultaneous Immunization

Advisory Committee on Immunization Practices. MMWR 2002; 51(RR-2):1-35 ftp.cdc.gov/pub/Publications/mmwr/rr/rr5102.pdf


- "Experimental evidence + extensive clinical experience strengthen scientific basis for administering vaccines simultaneously. ... Simultaneous administration critical when preparing for foreign travel + if uncertainty exists that person will return for further doses of vaccine."

Armed Forces Epidemiological Board (AFEB), Symposium on Simultaneous Immunization, Feb 2004:

- www.ha.osd.mil/afeb/meeting/021704meeting/default.cfm
- www.ha.osd.mil/afeb/2004/2004-04.pdf
- 'support the practice of concurrent immunization'
- offers 'strategies to ↓ concurrent vaccinations, minimize discomfort'


Bibliography on simultaneous vaccinations: 94+ articles

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 **Hotopf, et al. BMJ 2000**


- Hotopf M, David A, Hull L, et al. Role of vaccinations as risk factors for ill health in veterans of the Gulf war: Cross sectional study. *BMJ* 2000;320:1363-7.
- Multiple vaccinations given in a theater of war, but not multiple vaccinations given before deployment, associated with multi-symptom illness, fatigue, psychological distress, health perception, and physical functioning.
- Analysis limited to veterans who kept vaccination records.
- Exposures other than vaccination not controlled, except pesticide use. Anthrax vaccine was not analyzed independently.
- Authors recommend Armed Forces be vaccinated before deployment: "... folly to allow service personnel to be committed to a modern battlefield without all necessary means of protection against endemic infection and biological weapons."
- Shaheen, editorial, *BMJ* 2000;320:1351-2 evidence "inconclusive," design limitations, contrary findings.

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 **Length of Anthrax Vaccine Safety Studies**


	Surveillance points <u>after each dose</u>	Total surveillance <u>after dose # 1</u>
Fort Bragg	0, 1, 2, 3, 7, 30 days	= 30 days
RIID DR-RC	0, 1, 2, 3, 7, 30 days	= 6 months
Korea	2 weeks to 5 months	= 6 months
ACC-Langley	n/a	6 months
USAF Vision	n/a	≥ 6 months
Langley AFB	n/a	≥ 6 months
VAERS / AVEC	n/a	minutes to years
Canada	n/a	8 months after return
Tripler (TAMC)	≥ 7 days	≥ 1 year
Brachman	24, 48 hours	≥ 1.5 years
Inpt / Outpt Cohort	n/a	≥ 6 to 18 months
CDC DR-RC	days 2, 14, 14-28	3.5 years
Disability Evaluation	n/a	4.25 years
Fort Detrick long-term-99	n/a	27 years
Fort Detrick long-term-142	n/a	15 to 55 years (mean 43)

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 **Disability Discharge Evaluations**

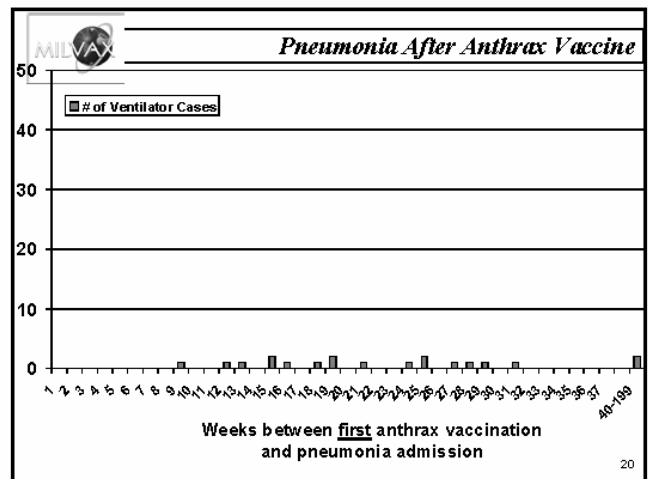
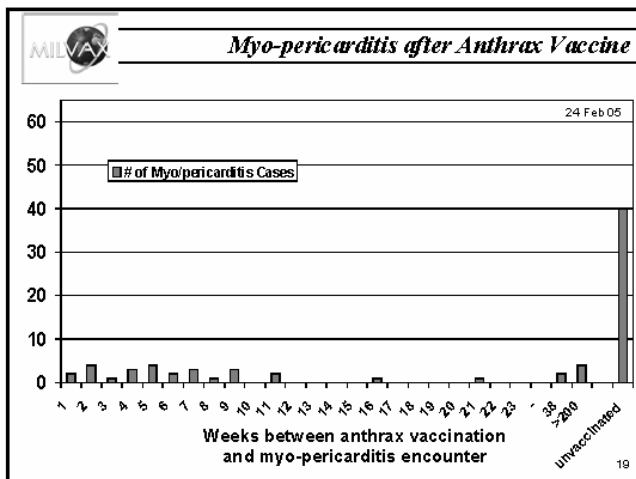
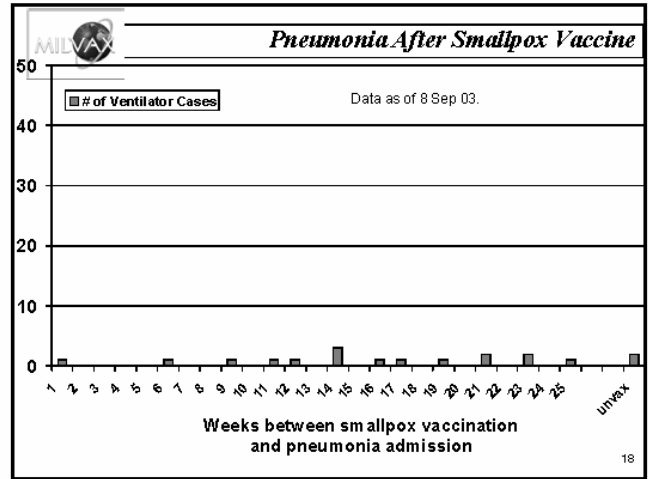
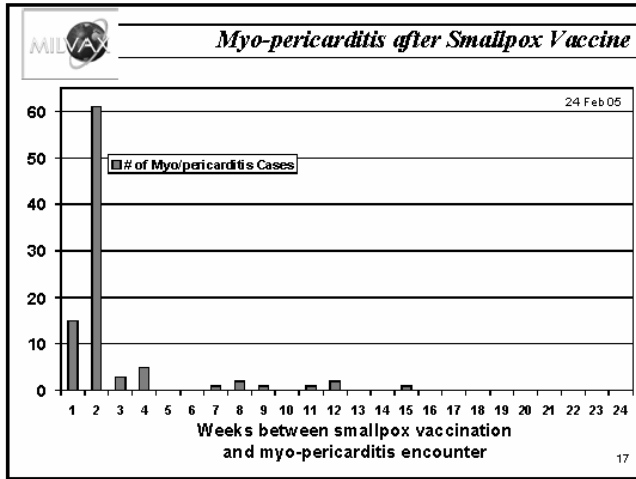
- Sulsky SI**, et al. Disability among U.S. Army personnel vaccinated against anthrax. *Journal Occupational & Environmental Med* 2004;46:1065-1075.
- Subjects:** U.S. Army personnel receiving ≥ 1 dose of anthrax vaccine adsorbed (AVA) between Mar 98 and Feb 02 vis-à-vis disability evaluation.
- Methods:** 29,332 disability evaluations among 716,833 active-duty Soldiers (154,456 vaccinated) over 4.25 years. Cox proportional-hazard models for risk of disability evaluation.
- Results:** Adjusted hazard ratio (HR) 0.96 (95% CI: 0.92, 0.99). Unadjusted rates: 140 per 100,000 person-months if unvaccinated, 68 per 100,000 person-months if anthrax-vaccinated.
- Separate adjusted HRs for men, women, permanent and temporary disability, musculoskeletal and neurological conditions similar, 0.90 to 1.04. Latency assumptions did not affect results.
- Conclusion:** Anthrax vaccination does not increase risk of disability evaluation, nor granting of disability finding.


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 **Long-term Safety Data: Lab Workers**

- Pittman PR**, et al. Long-term health effects of repeated exposure to multiple vaccines. *Vaccine* 2004;23:525-36.
- Workers:** 155 former biolab workers, 1943 to 1969, median 154 vaxtns or skin tests, median 17.3 y elapse. 92% received anthrax vaccine, 1943 to 1996. Interval from 1st vaccination to survey was 15 to 55 y (mean 43.1 y). Mean age: 69 years old.
- Controls:** 265 community controls from central Maryland matched on age, ethnicity and gender.
- Results:** Lab workers reported fatigue more than controls, but fatigue not associated with # of injections, # of vaccines, or time. No differences for self-reported medical conditions. Several laboratory abnormalities were more common in workers, but none clinically significant. Frequency of monoclonal spikes or paraprotein peaks (12.5% vs 4.5%), but no association with lifestyle, vaccine exposure, or medical conditions.
- Conclusion:** Intensive vaccination is not associated with an elevated risk of disease or medical condition.


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 ***Squalene as an Adjuvant***

Squalene is an oil. Produced in human liver, required for life.
Squalene naturally present in blood at 250 parts per billion (ppb). Fingerprint oils. Food. Supplements (olive oil).
Squalene alone may induce antibodies, but it is not an adjuvant (help antigens) by itself.
Squalene needs to be in the form of an emulsion (like mayonnaise) to be an adjuvant.
To be an adjuvant, squalene needs to be present at 1% to 5%
10,000,000 parts per billion (1%) to
50,000,000 parts per billion (5%)
FluAd (Italian influenza vaccine), given to > 10 million people, contains MF59 adjuvant, which includes 1.95% squalene, 19,500,000 parts per billion

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 ***Squalene and Squalene Tests***


A. SRI tests 17 lots of anthrax vaccine, all negative. Test capable of detecting as little as 140 ppb. Spanggard et al, 2002

B. FDA tests 3 vaccines: diphtheria, tetanus, anthrax. Finds squalene in each at 10 to 83 ppb. Tells Congress: "trace, naturally occurring, safe"

C. SRI improves test. Tests 33 lots: no squalene in 32 lots. Squalene in one lot at 1 to 9 parts per billion, or 1 to 9 parts per 1,000,000,000. Manuscript in progress.

Summary: Squalene not added as adjuvant to any US-licensed vaccine. Trace quantities may be present, concentration less than naturally present in human blood

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 ***Antibodies that Bind Squalene***

A1. Asa, Garry, et al. reported anti-squalene antibodies in Gulf War veterans. *Vanity Fair* 1999. *Exp Molec Path* Feb 2000.


IOM: "...does not regard study as providing evidence that investigators successfully measured antibodies to squalene..."

A2. *Exp Molec Path* Aug 2002. Test positive: 8/25 vaccinees, 3/19 unvaccinated. Antibodies associated with specific lots.

B1. Matyas, Alving, et al. *J Immunol Methods* Apr 2000. Mice given 71% squalene make squalene-binding antibodies. Antibodies don't cross react with squalene or cholesterol.

B2. *J Immunol Methods* Mar 2004. Squalene antibodies found: 0% of Fort Knox blood donors, 7.5% of Fort Detrick alumni, 15% of Frederick civilians. Conclusion: age-related effect.

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 ***Our Responsibility***

- **"Vaccines, of one sort or another, have conferred immense benefit on mankind but, like aeroplanes and motor-cars, they have their dangers . . . it is for us, and for those who come after us, to see that the sword which vaccines and antisera have put into our hands is never allowed to tarnish through over-confidence, negligence, carelessness, or want of foresight on our part."**

- The Hazards of Immunization, Sir Graham Wilson, 1967

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